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Suppression of the ethanol withdrawal syndrome by aliphatic diols

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20. ABSTRACT (continued)

administered intragastrically, were effective without inducing intoxication. Furthermore, the withdrawal-suppressing potencies of these drugs were related to their ability to partition into membranes, the same property that determines their potency as depressants. Two halogenated hydrocarbons, which are amphiphiles like alcohols and diols, were both able to suppress the withdrawal syndrome, although several aliphatic hydrocarbons could not. The data suggest that short-chain aliphatic alcohols and diols may have a common site of action, possibly in a region in membranes near the aqueous membrane interphase.

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Suppression of the Ethanol Withdrawal Syndrome by Aliphatic Diols¹

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ABSTRACT

Hunt, Walter A. and Edward Majchrowicz: Suppression of the ethanol withdrawal syndrome by aliphatic diols. *J. Pharmacol. Exp. Ther.* 213: 9-12, 1980.

Considerable evidence both *in vitro* and *in vivo* suggests that alcohols exert their intoxicating properties through an interaction with membranes. A wide range of alcohols and diols with divergent structures induce a virtually identical spectrum of intoxication signs. Because of their pharmacological similarities to ethanol, a number of aliphatic diols were tested to determine whether this class of compounds may have efficacy in suppressing the ethanol withdrawal syndrome in rats. All of the

diols tested, when administered intragastrically, were effective without inducing intoxication. Furthermore, the withdrawal-suppressing potencies of these drugs were related to their ability to partition into membranes, the same property that determines their potency as depressants. Two halogenated hydrocarbons, which are amphiphiles like alcohols and diols, were both able to suppress the withdrawal syndrome, although several aliphatic hydrocarbons could not. The data suggest that short-chain aliphatic alcohols and diols may have a common site of action, possibly in a region in membranes near the aqueous membrane interphase.

The primary effect of ethanol has been presumed to be through an interaction with membranes, although the exact mechanism has not been elucidated (Kalant, 1971; Grenell, 1972; Hunt, 1975; Chin and Goldstein, 1977). However, it is generally believed that this interaction is through some physicochemical alteration in membrane structure rather than through the classic drug-receptor model. Both *in vitro* and *in vivo* studies have indicated that the biological effects of alcohols are related to their ability to partition into membranes and not to some unique structure of the drug molecule or its metabolic effects (Brink and Pasternak, 1948; Rang, 1960; Lindbohm and Wallgren, 1962; Israel *et al.*, 1965; Majchrowicz, 1965; McCreery and Hunt, 1978). Furthermore, amphiphilicity of alcohols may be an important property in determining their ability to induce intoxication since 1) alcohols and aliphatic hydrocarbons with membrane/buffer partition coefficients greater than 20 to 50 exhibit decreasing potencies and 2) other nonalcoholic amphiphiles such as propylene glycol and propanethiol are effective intoxicants (McCreery and Hunt, 1978).

The long-term use of ethanol can result in the development of tolerance and physical dependence both in man (Victor and Adams, 1953; Mendelson, 1964; Gross *et al.*, 1974) and in experimental animals (Freund, 1969; Ellis and Pick, 1970; Goldstein

and Pal, 1971; Pieper *et al.*, 1972; Majchrowicz, 1975; Majchrowicz and Hunt, 1976). Since a wide variety of alcohols and diols have been shown to exert behavioral effects similar to those of ethanol (McCreery and Hunt, 1978), these compounds may be effective in antagonizing the ethanol withdrawal syndrome. In a recent report 1,3-butanediol was tested for this purpose (Majchrowicz *et al.*, 1976). A 4 g/kg oral dose was found to suppress the tremulous and convulsive components for 1 to 5 hr without inducing intoxication.

In the present investigation a number of other diols were tested to determine if they also would be effective in suppressing the ethanol withdrawal syndrome. In addition, the potencies of these compounds were compared to their partition coefficients to determine if partitioning into membranes is an important property in influencing potency.

Methods

Male Sprague-Dawley rats (150-250 g) were rendered ethanol-dependent by the method of Majchrowicz (1975). This involved the daily administration of 9 to 13 g/kg as a 20% (w/v) solution of ethanol in four to six divided doses for 4 days. Animals were usually dosed 7:00, 12:00, 18:00 and 24:00 hr with booster doses at 10:00 and 15:00 hr if needed. The doses given were related to the degree of intoxication present, as follows: no signs of intoxication, 5 g/kg; sedated, 4 g/kg; ataxia 1, 3 g/kg; ataxia 2, 2 g/kg; and ataxia 3, 1 g/kg. No dose was given to animals with loss of righting reflex or coma. For specific definitions of each sign of intoxication, see Majchrowicz (1975) and Majchrowicz and Hunt (1976). The last dose of ethanol marked the initiation of the withdrawal period, during which time two successive phases emerged (Majchrowicz,

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1975). During the early prodromal detoxication phase, animals exhibited signs of ethanol intoxication, the severity of which decreased gradually as blood ethanol concentrations declined. When the blood ethanol concentrations approached 150 to 100 mg/dl, there was a progressive development of typical signs of the ethanol withdrawal syndrome, an expression of ethanol dependence. This was characterized by the appearance of hyperactivity; tremors of the tail, caudal region and head; general tremors; rigidity of the tail and body; wet shakes and chattering teeth; bizarre behavior; induced convulsions and running episodes; and spontaneous convulsions of the clonic-tonic type.

The development and progression of the entire withdrawal period from the prodromal detoxication phase through the withdrawal syndrome was systematically evaluated at hourly intervals by open field observations and tactile evaluation of the behavioral and neurological signs during the first 7 to 24 hr of the withdrawal period. All the above-listed signs of the ethanol withdrawal syndrome were routinely recorded, yet, for the purpose of scoring the effectiveness of the compounds in suppressing the withdrawal syndrome, only tremors were used because tremors are the most characteristic, unambiguous and most frequently observed sign of the withdrawal syndrome in humans (Victor and Adams, 1953; Mendelson, 1964). In addition, tremors were also found to be the most reliable sign of the ethanol withdrawal syndrome in animals (Ellis and Pick, 1970; Goldstein and Pal, 1971; Majchrowicz, 1975) and most suitable for quantification in our animal model of physical dependence on ethanol (Majchrowicz *et al.*, 1976). Tail, caudal, head and general tremors were rated as mild (rating 1), moderate (rating 2), or severe (rating 3), respectively, as described previously (Majchrowicz, 1975; Majchrowicz *et al.*, 1976), and the sum of the ratings was used as the withdrawal score. The total maximum possible score any animal could attain for tremors was 12. In general, the severity of tremors of the tail, caudal region and general tremors ranged between 1 and 3, whereas those of the head usually were not higher than 2.

When the withdrawal score reached at least 6, a test compound, dissolved in distilled water or peanut oil, was administered intragastrically. Drugs were administered by someone other than the observer who did not know what, if any, compound was given. Three to six doses were used, and the one that blocked the tremulous stage for at least 2 hr without inducing any of the signs of intoxication as listed above was estimated from dose-response relationships. Seven to 18 rats were used to establish the potency of a compound. Sample scores can be found in table 1.

Membrane/buffer partition coefficients were obtained from a previous report (McCreery and Hunt, 1978) as calculated from the equations of Fujita *et al.* (1964).

Results

Fifteen compounds were tested for their ability to block ethanol withdrawal signs. Most of them were diols of different structural types: *e.g.*, terminal, primary-secondary, secondary and tertiary diols. In addition, two alkyl halides, three hydrocarbons, ethanol and 1-propanol were also evaluated.

All of these compounds except the hydrocarbons, which induced no obvious response at the doses tested, were able to block the withdrawal syndrome without inducing intoxication (table 2). In fact, they reacted identically with no significant differences among them, except for the dose. This varied from 10.3 mmol/kg for 2,5-dimethyl-2,5-hexanediol to 44.4 mmol/kg for 2,3-butanediol.

To determine whether the dose was related to the ability of the compound to partition into membranes as it does for inducing intoxication (McCreery and Hunt, 1978), the log of the effective dose that blocks the tremulous stage of the withdrawal syndrome was plotted against the log of the membrane/buffer partition coefficient. As can be seen in figure 1, a linear relationship was obtained ($r = -0.88$; $b = -0.45$; $t = 5.06$; $df = 8$;

TABLE 1
Effect of 1,3-butanediol on ethanol withdrawal scores

Dose	Withdrawal Score ^a				Intoxication ^b
	Time after treatment				
	0 hr	1 hr	2 hr	3 hr	
g/kg					
2	7.3	2.3	1.5	5.0	No
3	7.3	2.0	2.0	1.5	No
4	6.5	0	0	0	No
6	5.0	0	0	0	Yes

^a Withdrawal scores are the sums of the ratings of tail, caudal, head and general tremors (see "Methods").

^b Intoxication is present when any of the signs of intoxication as listed in "Methods" is present.

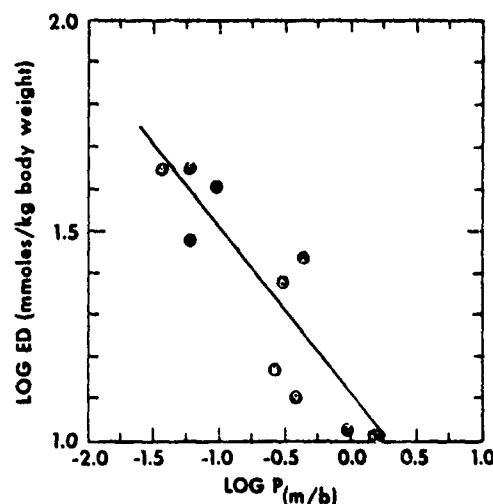


Fig. 1. Plot of the logarithm of the potency to suppress the tremulous stage of the withdrawal syndrome (ED) as a function of the logarithm of the membrane/buffer partition coefficient ($P_{m/b}$) (—). Numbers inside data points refer to the respective compound listed in table 2.

$p < .001$). From this relationship, it is presumed that hydrocarbons do not interact with membranes in the same manner as diols since doses 5 to 10 times higher than values predicted from the extrapolated regression line were ineffective.

Discussion

A wide variety of alcohols and diols have been shown to have the common feature of inducing a behavioral spectrum of intoxication virtually identical to that of ethanol (McCreery and Hunt, 1978). Although the three-dimensional structure does not appear to play a role in their action, except in determining potency, it does influence the amount of drug that can dissolve in membranes based on the drug's membrane/buffer partition coefficient. In essence this means that a certain concentration of the alcohol must be attained in excitable membranes before intoxication can be manifested, similar to that for anesthetics (Meyer and Gottlieb, 1926; Meyer, 1937).

Since similar behavioral effects are observed with alcohols and diols of such diverse structures, there may be a common site of action within membranes (McCreery and Hunt, 1978). Since ethanol blocks the ethanol withdrawal syndrome, any of these compounds might also be expected to be effective. The present study demonstrates that, in addition to short-chain

TABLE 2

Potencies of various compounds to either block the tremulous stage of the ethanol withdrawal syndrome without inducing intoxication or induce ataxia

ED_{50W} refers to the effective oral dose necessary to block the tremulous stage of the ethanol withdrawal syndrome without inducing intoxication (see "Methods"). ED_{50A} refers to the effective intraperitoneal dose necessary to induce a defined state of ataxia. P_{m/b} refers to the membrane/buffer partition coefficient also obtained from McCreery and Hunt (1978).

	ED _{50W} mmol/kg p.o.	ED _{50A} ^a mmol/kg i.p.	P _{m/b}
Alcohols			
1. Ethanol CH ₃ CH ₂ —OH	40.2	32.6	0.096
2. 1-Propanol CH ₃ CH ₂ CH ₂ —OH	27.5	13.3	0.438
Diols			
3. 1,2-Butanediol $\begin{array}{c} \text{HO} \\ \\ \text{HO}-\text{CH}_2-\text{CH}-\text{CH}_2-\text{CH}_3 \end{array}$	30.4	32.6	0.060
4. 1,3-Butanediol $\begin{array}{c} \text{HO} \\ \\ \text{HO}-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}_3 \end{array}$	44.4	65.4	0.060
5. 2,3-Butanediol $\begin{array}{c} \text{HO} \quad \text{OH} \\ \quad \\ \text{CH}_3-\text{CH}-\text{CH}-\text{CH}_3 \end{array}$	44.4	43.5	0.088
6. 1,5-Pentanediol HO—CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ —OH	24.0	33.7	0.303
7. 1,6-Hexanediol HO—CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ —OH	10.6	11.4	0.957
8. 2,5-Hexanediol $\begin{array}{c} \text{HO} \quad \text{HO} \\ \quad \\ \text{CH}_3-\text{CH}-\text{CH}_2-\text{CH}-\text{CH}_3 \end{array}$	12.7	8.3	0.381
9. 2,3-Dimethyl-2,3-butanediol $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ \text{CH}_3-\text{C}-\text{C}-\text{CH}_3 \\ \quad \\ \text{OH} \quad \text{OH} \end{array}$	14.8	14.8	0.264
10. 2,5-Dimethyl-2,5-hexanediol $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ \text{CH}_3-\text{C}-\text{CH}_2-\text{CH}_2-\text{C}-\text{CH}_3 \\ \quad \\ \text{OH} \quad \text{OH} \end{array}$	10.3	8.3	1.52
Alkyl halides			
11. 1-Chloropropane CH ₃ CH ₂ CH ₂ —Cl	31.8	10.3	
12. 2-Bromopropane $\begin{array}{c} \text{Br} \\ \\ \text{CH}_3-\text{CH}-\text{CH}_3 \end{array}$	30.5	10.2	
Hydrocarbons			
13. Pentane CH ₃ CH ₂ CH ₂ CH ₂ CH ₃	>55.0	>40.0	63.2
14. Hexane CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	>11.5	>11.5	200
15. Heptane CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	>10.0	>10.0	632

^a These values were obtained from McCreery and Hunt (1978).

aliphatic alcohols, a representative number of diols, when given orally, were all capable of suppressing the withdrawal syndrome without inducing intoxication. Furthermore, the potency of these diols was directly related to their membrane/buffer partition coefficients, in the same way as their potency for inducing intoxication (McCreery and Hunt, 1978). This suggests that there may be a common site of action for suppressing the withdrawal syndrome, presumably at the same site as for the induction of intoxication.

The ability of diols to suppress the ethanol withdrawal syndrome indicates that these compounds may also interact in

some way with the same site(s) responsible for the development of physical dependence on ethanol. McComb and Goldstein (1979a,b) have reported some interesting experiments involving the induction of physical dependence on *t*-butanol. They showed that not only could *t*-butanol induce a state of dependence virtually identical to that of ethanol, but also the two compounds could be administered sequentially and produce the same magnitude of dependence as either compound alone over the same total time period. No withdrawal syndrome is observed until after the removal of the second drug. Since a wide variety of alcohols and diols share common pharmacological

properties (McCreery and Hunt, 1978), and can suppress an ethanol withdrawal syndrome, they may all exhibit cross-dependence arguing further for a common site of action.

It has been suggested previously that the site of action of alcohols and diols might be in the vicinity of the membrane/aqueous interphase of neuronal membranes (McCreery and Hunt, 1978). This conclusion is based on the observation that the induction of ataxia is inversely correlated to the membrane/buffer partition coefficient as long as the coefficient does not exceed 20 to 50. Compounds with higher coefficients lose potency or are ineffective. The finding that aliphatic alcohols and diols and alkyl halides can suppress the ethanol withdrawal syndrome, although aliphatic hydrocarbons cannot, provides further support that these compounds act as a result of their amphiphilic nature and at a specific level in the membrane structure even if not through binding to a specific receptor substance.

In summary, we have demonstrated that a variety of aliphatic diols administered intragastrically can suppress the ethanol withdrawal syndrome without inducing intoxication. The gross behavioral effects are identical and their potencies are directly related to their ability to partition into membranes. These data suggest that there may be a common site of action for all these compounds. Although therapeutic usefulness has not been established, drugs of this type may have some efficacy in the treatment of the ethanol withdrawal syndrome and should be further investigated.

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